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Use of the Platelet Histogram Maximum in Evaluating Thrombocytopenia

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The purpose of this study was to compare the mean platelet volume (MPV) and the highest peak of the platelet volume distribution curve (maximum of the platelet histogram) with regard to their ability to discriminate between thrombocytopenia due to decreased platelet production or increased platelet destruction. A total of 156 children were studied. Twenty-eight had a diagnosis of idiopathic thrombocytopenic purpura (ITP) and 128 had a low platelet count due to decreased production. MPV and maximum of the platelet histogram were obtained by using the Coulter Counter Max M (Coulter Diagnostics, Hialeah, FL). A comparison of the sensitivity and specificity for the MPV and the maximum of the histogram has been made using the method of the receiver operating characteristic curves. The results show that the maximum of the histogram is superior to the MPV and is a highly effective test for the evaluation of thrombocytopenia. We recommend the use of the maximum rather than the MPV to help distinguish between ITP and thrombocytopenia secondary to decreased platelet production. Am. J. Hematol. 60:19–23, 1999. © 1999 Wiley-Liss, Inc.

Key words: Idiopathic thrombocytopenic purpura (ITP); mean platelet volume (MPV); platelet histogram

INTRODUCTION

Traditionally, thrombocytopenia is divided into states of increased platelet destruction or loss, generally associated with increased production, and conditions of decreased platelet production. Included in the evaluation of thrombocytopenia have been the megathrombocyte index and the mean platelet volume (MPV). The megathrombocyte is a platelet larger than 3.0 microns. A high percentage of such platelets is considered evidence of increased production [1,2]. The MPV is an automated measurement of the platelet volume and has been reported to be useful for this evaluation [3–7]. However, it has also been shown that the platelet size does not always correlate with platelet age [8]. In this study a new measure, the maximum of the platelet histogram or, in other words, the highest peak of the volume distribution curve, was used as a parameter for the evaluation of thrombocytopenia and was compared with the MPV.

The MPV has been shown to be stable in an individual [9]. Additionally, an inverse relation between MPV and platelet count has been defined [10–12]. Finally, the reproducibility of the mathematical algorithm of the platelet volume distribution and its accuracy are established [13]. Vukelja et al. [14] have shown the MPV to be the better test for the evaluation of thrombocytopenia than the megathrombocyte index. Our study follows their approach to compare the two parameters. One of the problems with using the MPV is that it can be influenced by a variety of artifacts. Every particle under 20 fl will be counted as a thrombocyte. Thus, cell fragments from erythrocytes or leukemic blasts will alter platelet count and MPV artificially. The occurrence of erroneously high platelet counts and the alteration of the volume distribution, and by this the alteration of the MPV, have been described [15–17]. Such results can mislead the clinician using the MPV to evaluate thrombocytopenia. Therefore automated platelet volumes should be read with caution. Sassier and Breillot [13] suggested dividing platelet histograms into three groups: One with platelets smaller than 2 fl, one with platelets larger than 20 fl, and a third

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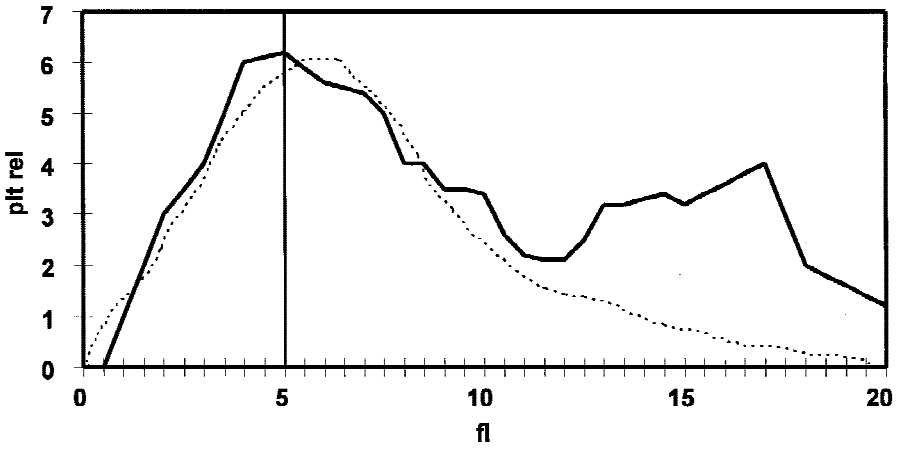


Fig. 1. (——) The platelet histogram of a child with acute lymphoblastic leukemia. Platelet count: 31,000/μl; MPV 10.0 fl; maximum at 5 fl (vertical line). The irregular shape and the second peak at 17 fl is likely to be caused by blast fragments which also raise the MPV, while the maximum stays unaltered. (- - - -) indicates the histogram of a healthy child.

group with neither platelet size. However, application of this method to our study was not helpful, as children with increased platelet destruction or decreased platelet production fell into all three groups. In this study we assessed the role of the maximum of the platelet volume distribution for evaluating thrombocytopenia, as this measurement would be less influenced by red or white cell fragments or other artifacts. Figure 1 shows the histogram of a child with acute lymphoblastic leukemia. While the MPV is unusually high (10.0 fl) because of the fragments counted as thrombocytes, the maximum is not altered (5 fl).

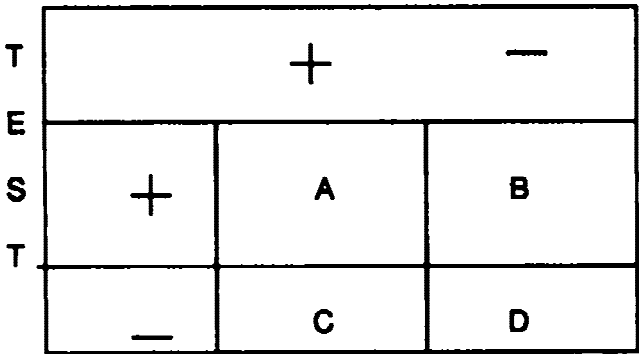
We divided patients according to their diagnosis into two groups: Hypoproductive thrombocytopenia (leukemia, on chemotherapy, aplastic anemia) or hyperproductive thrombocytopenia (idiopathic thrombocytopenic purpura) (ITP). Means, sensitivity, specificity, receiver operating characteristic (ROC) plot, and correlations of the MPV and of the histogram maxima are used to measure the clinical utility of these parameters in the evaluation of thrombocytopenia.

MATERIALS AND METHODS

The study population consisted of patients seen in the hematology/oncology clinic of the Rhode Island Children's Hospital, Providence, RI. Patients had thrombocytopenia defined as platelet counts <130,000/μl. The hyperproductive group consisted of patients with a diagnosis of ITP. ITP was defined as the sudden onset of significant thrombocytopenia with the absence of other causal diseases as determined by history, physical exam, complete blood count, peripheral blood smear, and when appropriate, bone marrow aspiration/biopsy and immunologic studies. Hypoproductive thrombocytopenia was present in patients receiving chemotherapy or having aplastic anemia or acute leukemia. Thrombocytopenias of unknown origin were not included in this study.

Measurements were performed on a Coulter Counter model Max M (Coulter Diagnostics, Hialeah, FL). The system provides the clinician with the MPV and the histogram. Maxima were extracted from the histograms in half-femtoliter steps.

Sensitivity was defined as the number of true positive out of the disease positive A/(A + C). A stands for the number of patients that have the disease and are also detected by the chosen mean of discrimination, while C stands for the number of patients that have the disease, but are not detected by the given test. Thus (A + C) equals the total number of patients with the disease. Specificity was defined as the number of the true negative out of the disease negative D/(B + D). D symbolizes the number of patients that do not have the disease and are correctly identified, while B stands for the number of patients who do not have the disease, but are incorrectly identified by the given test as having the disease. Thus (B + D) equals the total number of patients that do not have the disease the observer is looking for [18].



A comparison of the sensitivity and the specificity for the MPV and the maxima has been made using the method of the ROC curves (Fig. 2) [19]. These plots were developed in the 1950s for evaluating radar signal detection. Only recently have they become widely used in medicine. The ROC plot is obtained by plotting sensitiv-

TABLE I. Patients, Mean Values, and Standard Deviation*

State of production	n	MPV ± SD	Maxima ± SD
ITP	28	10.02 ± 0.58	7.90 ± 0.93
Decreased production	118	8.05 ± 0.96	5.12 ± 0.71

*MPV, mean platelet volume, ITP, idiopathic thrombocytopenic purpura, SD, standard deviation.

ity against 1-specificity for the complete range of decision thresholds. As stated before, sensitivity gives the probability of getting the result (here: maximum or MPV) if the patient truly has the condition of interest (here: thrombocytopenia due to increased platelet destruction) while 1-specificity gives the corresponding probability if the patient does not have the condition of interest or, in other words, the false positive. The performance of a test is assessed by the area under the ROC curve. This area gives the probability that a patient with the disease (here: ITP) has a higher value of the measurement (here: MPV or maximum) than a person without the disease. A test that is completely useless would give the diagonal shown in Figure 2. A test that perfectly discriminates between the two patient groups would show a line that coincided with the left and top side of the plot. An ROC plot is especially helpful to compare two methods of discrimination. By graphing two ROC plots together, two diagnostic tests can be compared. The relative positions of the plots indicate the relative accuracies of the tests. A plot lying above and to the left of another plot indicates greater observer accuracy [20].

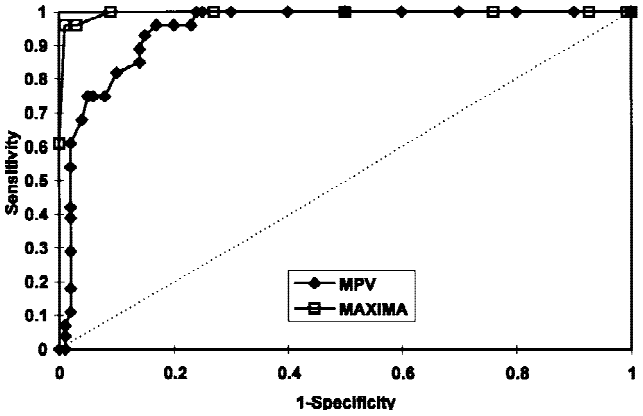


Fig. 2. ROC curve comparing MPV and maxima. The diagonal shows a valueless test.

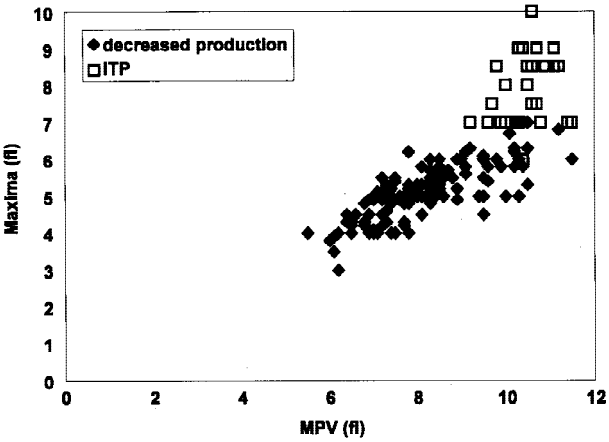


Fig. 3. Scatter plot of the correlation of the MPV and the maxima.

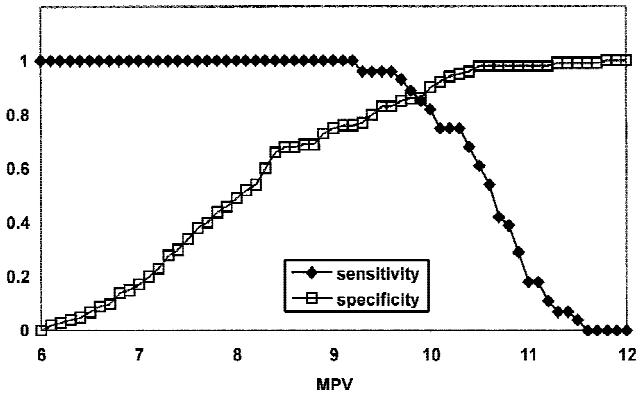


Fig. 4. Sensitivity and specificity for a range of the MPV (6–12 fl).

RESULTS

Patients

A total of 156 patients were studied. Age ranged from 4 yr to 19 yr with a mean age of 7.7 years. Twenty-eight had a diagnosis of ITP and 128 had thrombocytopenia due to decreased platelet production.

Mean Values

The mean values for the MPV and the maxima as well as the standard devitions are listed in Table I. The mean values for the MPV and the maxima are significantly different for ITP vs. decreased production ($P < .0001$).

Correlation

The correlation between MPV and maxima is shown on the scatter diagram in Figure 3.

Sensitivity and Specificity

The sensitivity and specificity are shown in Figure 4 for a range of MPV and in Figure 5 for a range of the maxima. The ranges were chosen in a way that all MPV/maxima were included. If the MPV $\geq$ 8.3 fl, then 100% of the ITP patients will be detected (sensitivity = 1), but only 60% of the patients with hypoproductive thrombocytopenia will be excluded (specificity = 0.6). If the MPV is chosen to be $\geq$9.4 fl, then 96% of the ITP patients will be detected and 80% of the patients with

TABLE II. Sensitivity and Specificity Using the MPV/Maxima*

MPV	Sensitivity	Specificity	Maxima	Sensitivity	Specificity
6	1	0	3	1	0
7	1	0.17	5	1	0.5
8	1	0.49	5.5	1	0.73
9	1	0.75	6	1	0.91
9.3	0.96	0.77	6.5	0.96	0.97
9.4	0.96	0.8	7	0.96	0.99
9.7	0.93	0.85	7.5	0.61	1
10	0.82	0.9	8	0.54	1
10.5	0.61	0.98	8.5	0.46	1
11	0.18	0.98	9	0.19	1
11.8	0	1	10.5	0	1

*MPV, mean platelet volume.

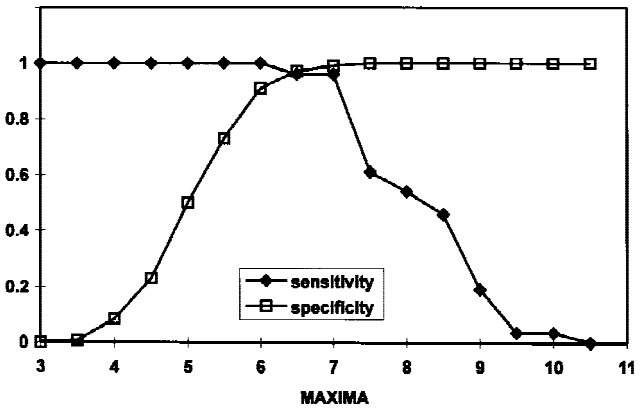


Fig. 5. Sensitivity and specificity for a range of the maxima (3–11 fl).

hypoproductive thrombocytopenia will be excluded. If the maxima are chosen to be ⩾6 fl, 100% of the ITP patients will be detected and 9% of the patients with hypoproductive thrombocytopenia will be excluded. If the maximum is ⩾7.5, then all of the patients with hypoproductive thrombocytopenia will be excluded, but only 61% of the ITP patients will be detected. Some of these data are listed in Table II.

The ROC curves, shown in Figure 2, demonstrate that the maximum is superior to the MPV in discriminating between ITP and hypoproductive thrombocytopenia.

DISCUSSION

There are several diagnostic methods to help the clinician discriminate whether a low platelet count in a patient is caused by decreased production or increased destruction or loss. Size of the thrombocytes has been used by Garg et al. [1,2] who demonstrated that the megathrombocyte percentage in the peripheral blood smear correlates with the number of megakariocytes in a bone marrow aspirate, and thus with a state of hyperproduction. Also it has been demonstrated that the percentage of megathrombocytes increases in states of hyperproduction. More recently the MPV has been shown to be useful for detection of platelet production states [3–7]. Vukelja et al. [14] compared the MPV test to the megathrombocyte index in 1993 and found the former to be a better discriminant between production states. The MPV, however, has been shown to be frequently influenced and altered by e.g., debris or cell fragments [15–17], and in cases with severe autoimmune thrombocytopenia, by small particle spikes [21,22]. We were interested in evaluating the maximum of the platelet volume distribution histograms, as this value is not easily influenced by these artifacts. The Coulter systems provide the clinician with these histograms. Each maximum is easy to measure as femtoliters are given in millimeters. Our study demonstrates that the maximum provides a better discrimination than the MPV. A question then arises as to the best cut-off point for clinical use. Altman and Bland [18] stated that the point with the highest sum of sensitivity and specificity is not necessarily optimal. Perhaps the most important function of any test used to evaluate thrombocytopenia is not solely to be sensitive enough to capture the vast majority of hyperproductive states, such as ITP, but to be specific enough to essentially rule out hypoproductive cases, such as leukemia. As shown in Table 2, choosing a maximum of seven or greater will detect 96% of the cases of ITP while excluding 99% of the hypoproductive situations. This measurement can aid the clinician in the analysis of thrombocytopenia states and help support decisions regarding the need for bone marrow studies. The MPV in this study discriminated better between thrombocytopenic states than in the study of Vukelja et al. [14] A possible explanation for this finding is that Vukelja et al. also included patients with hypersplenism and myeloproliferative disorders into their group of hyperproductive thrombocytopenias, while our population included only ITP. Nevertheless, the advantage of using the maximum rather than the MPV is well illustrated in those cases of hypoproduction with a low maximum and a high MPV (Fig. 1), where the irregular shape of the histogram is probably evidence of artifacts that influence the MPV. This is particularly true in patients with very low platelet counts, where the artifacts alter the MPV even stronger, because as the number of thrombocytes decreases, the influence of artifacts increases.

We conclude that the maximum is highly useful in discriminating between different thrombocytopenic states and because of this it is superior to the MPV.

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